"TEMPOSIL" A NEW DRUG IN THE TREATMENT OF ALCOHOLISM

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Introduction

In the last decade the use of disulfiram (Antabuse) has considerably altered the treatment of chronic alcoholism. However, unpleasant side-effects of headache, metallic taste in the mouth, abdominal discomfort and impotence are found in patients on maintenance treatment with this drug and deters them from taking it (4, 10). Alcohol-disulfiram reactions can be accompanied by cardiac complications or sudden death (9, 11). Despite these difficulties alcoholics who take disulfiram regularly have better abstinence records than those who do not (15). Many reasons may be postulated for these results, but we have regarded the use of disulfiram as a means of providing a period of "forced" abstinence while the alcoholic is readjusting to the demands of resuming his job, family relations, etc. During this time some insight and understanding of the nature of his difficulties may be established. The remainder of this paper describes the investigation of a new substance, Temposil, which produces a similar effect to disulfiram.

Temposil was first described by Ferguson (5). It is essentially the calcium salt of carbimide, an industrial product long known for its ability to produce "mal rouge" in workmen exposed to it if they later drank alcohol. For medical use a highly purified preparation of carbimide is required with the addition of sufficient acid to the calcium carbimide to neutralize it and keep the pH of the medium between four and five. This is achieved by adding citric acid 2 parts by weight to one part of calcium carbimide.

As rapid absorption of carbimide from the stomach produces unpleasant direct effects on the C.N.S. the final tablet form used was of a "slow release" type.

Mode of Action

During the oxidation of ethyl alcohol acetaldehyde is produced. In normal human blood acetaldehyde is present in amounts of less than 0·05 mg. per 100 c.c. but after drinking alcohol blood acetaldehyde levels rise to 0·2–0·4 mg.

per 100 c.c. If a patient has previously had disulfiram or Temposil, after drinking alcohol blood acetaldehyde levels are markedly increased because these substances appear to inhibit enzymes needed for the oxidation of acetaldehyde (7, 8, 12, 13).

The effects of disulfiram were thought to be due only to increased blood acetaldehyde concentrations, but there is evidence to show that both disulfiram and Temposil alter the vascular reaction to acetaldehyde (5, 6, 12).

Method of Investigation

Patients treated with Temposil had been admitted to the alcoholic unit, St. Luke's Hospital, Middlesbrough and were chronic alcoholics within the definition of the World Health Organization Memorandum (1950) on this subject. They ranged in age from 23–59 years with an average age of 40. Thirty male and 3 female patients were treated during this investigation.

Before commencing treatment the following investigations were carried out:

1. Full physical examination.
2. Full blood count and film.
3. Urinalysis.
4. Liver function tests:
   (*a*) Plasma alkaline phosphatase.
   (*b*) Thymol turbidity.
   (*c*) Van Den Bergh reaction.
   (*d*) Total plasma bilirubin.
   (*e*) Urine for urobilinogen, urobilin and bilirubin.
5. Chest X-ray.
6. Some ten patients in the later stages of the investigation had E.C.G. recordings.

All the cases treated were in good health with normal laboratory findings at the time of the test reaction.

As in other investigations reported at that time initially patients were given Temposil in a dose of 50 mg. daily (1, 2, 14). At a later stage for reasons discussed below a dosage of 100 mg. of Temposil was used.

The technique adopted for each test reaction was as follows:

The patients were encouraged to take their ordinary meals before tests and as far as possible every attempt was made to minimize the artificial atmosphere associated with drinking in hospital. The alcohol used was always that of the patient's choice, since we had found previously that otherwise the alcoholic, with his great capacity for rationalization, frequently stated that the results of various treatments were caused by "the liquor not being the right stuff". The beverages used varied in their alcoholic content, but the amounts consumed were the equivalent of 15–90 c.c. of absolute alcohol. Alcohol was given at varying times ranging from 1–36 hours after taking Temposil. No reactions were observed where alcohol was given more than 30 hours after the last dose of Temposil.

In Table I symptoms described by the patients are listed according to the time of onset.

TABLE I

Number of patients on 50 mg. Temposil 12
Number of patients on 100 mg. Temposil 36
Amount of alcohol equivalent of .. .. .. 15–90 c.c. absolute alcohol

Symptoms	No. of Patients Reacting on Dosage:		Average Time of Onset in Minutes	
	50 mg.	100 mg.	50 mg.	100 mg.
1. Feeling of well-being	8	8	12	4
2. Feeling of warmth	9	34	12	8
3. Headache	5	18	49	15
4. Tightness in chest	5	25	32	16
5. Pain in chest and arm ..	1	4	45	16
6. Palpitations	9	32	28	17
7. Increased desire to drink ..	8	11	10	20
8. Paraesthesiae	2	5	16	31
9. Nausea	1	6	90	41
10. Shivering	1	9	60	54
11. Apprehension	1	17	45	56
12. Dizziness	1	7	70	56

In 12 patients given alcohol after taking 50 mg. of Temposil typical acetaldehyde reactions were observed, but this was marked in only one case. The most striking feature of these tests was that eight patients expressed feelings of well-being with increased desire to drink. Further alcohol (in five cases to the equivalent of 90 c.c. of absolute alcohol) did not intensify the acetaldehyde reaction. This response has not been reported elsewhere although it is of considerable importance in the use of Temposil in long-term treatment of alcoholism. The effects of 100 mg. doses of Temposil were further studied to see whether this factor could be modified or eliminated.

The pattern of alcohol-Temposil reaction is fairly constant in development and a brief account on each symptom and its correlation with physical findings will be made.

A feeling of well-being was an early symptom, more prominent in the 50 mg. group. After taking alcohol eight (66 per cent.) of these cases became elated, jocular and expansive in manner, a feature which persisted despite later development of an acetaldehyde reaction. Eight patients (22 per cent.) treated with 100 mg. of Temposil expressed similar feelings of well-being but this was sustained in only four cases when the reaction became more marked.

A feeling of warmth was the most common finding and was closely connected with the observed signs of flushing, urticaria and conjunctival injection.

Headache was usually described as beginning with hot tight sensations of frontal distribution, gradually developing to a more generalized throbbing ache which persisted for periods lasting up to six hours. This was the most prolonged effect of alcohol-Temposil reaction and would appear to suggest that the cerebral vessels develop a greater degree of sensitivity to acetaldehyde after Temposil than is observed in other parts of the cardiovascular system.

Tightness in the chest and throat was usually described as "difficulty in breathing in", the patients being aware of having to "push" air into the lungs. When these symptoms were prominent bronchospasm was noted on auscultation.

Pain in the chest and arm was found in four cases. These patients had complained of palpitation and tightness in the chest to a greater degree than average

before feeling pain. Pain was of a cramping nature and affected the whole chest wall at first. With continued fall in blood pressure the pain usually became more localized over the praecordium before radiating down the left arm. In one case the pain radiated down both arms with cramp-like sensations in the fingers. Three cases had cardiac irregularity at the same time, but this was not marked.

Palpitation was closely related to increase in the pulse rate and volume and was most marked in severe reactions.

Increased desire to drink was found in eight cases (66 per cent.) in the 50 mg. group. Eleven (30 per cent.) treated with 100 mg. Temposil showed increased desire to drink but this was sustained in only four cases (11 per cent.) when other features of the reaction became more marked.

Paraesthesiae were described in seven cases and usually as widespread tingling sensations affecting all parts of the body, particularly the extremities. This symptom was noted in association with an increased desire to drink.

Nausea was an infrequent finding of late onset, found in only two cases.

Shivering and a feeling of coldness were of late onset and were found only in severe reactions.

Apprehension was expressed by 18 patients and was associated with severe degrees of tightness and pain in the chest, shivering and shock. This was not, however, a very serious symptom except in one case where the total reaction was atypical, occurring two hours after taking alcohol.

Dizziness was described as a sense of haziness with a feeling that the room was no longer fixed and steady. Of late onset this symptom usually disappeared when the patient lay flat on the bed. In assessing the severity of a reaction dizziness was of little value, being marked in six cases where the general reaction was slight or moderate.

In Table II the physical signs observed are summarized according to the systems affected, but they also fall into a consecutive time sequence.

TABLE II

Signs	No. of Patients Reacting on Dosage:		Average Time of Onset in Minutes	
	50 mg.	100 mg.	50 mg.	100 mg.
1. Flushing	12	36	13	5
2. Urticaria	6	26	28	12
3. Conjunctival injection	3	25	33	15
4. Bronchospasm	1	17	20	15
5. Increased respiratory rate	—	4	—	25
6. Increased pulse rate	12	36	25	19
7. Change in blood pressure	7	31	35	40
8. Shock	1	6	70	60
9. Cardiac irregularity	—	5	—	75
10. Perspiration	3	8	23	25
11. Drowsiness	1	5	140	44

Flushing affected mainly the face, neck and upper trunk, but was also seen in the limbs. This was usually the first reaction, but the degree of flushing did not provide any accurate indication of later severity of response. Urticarial rashes appeared after flushing as scattered patches of map-like erythema on the trunk, arms and legs. No patient complained of pruritus or other abnormal sensation in the areas of urticaria which faded before the flushing subsided.

Conjunctival injection with lachrymation occurred less often, but gave a good indication of the severity of the reaction, which could be expected. Marked

reddening of the conjunctivae with free flow of tears was invariably associated with severe reactions.

These signs appear to have been produced both by direct action of increased acetaldehyde concentration and also by alteration of the vascular reaction to acetaldehyde.

Respiratory signs were difficult to assess since although patients commonly complained of tightness in the chest and breathing sounded laboured only four patients showed a definite increase of respiratory rate. A more common finding was bronchospasm, presumably a true allergic response of the respiratory passages to acetaldehyde. Perspiration was not common except in severe reactions.

Drowsiness was an infrequent finding of late onset lasting from 15–30 minutes.

Increase in pulse rate was found in every reaction and varied from a rise of 30 per minute to as much as 70 per minute. In general the greater the increase in the pulse rate, the more severe the reaction, but in some cases palpitation and increases of pulse rate of 40–60 beats per minute were found in otherwise slight reactions.

Changes in blood pressure followed a common pattern with a slight increase in diastolic pressure of 10–15 mm. Hg about 15 minutes after alcohol. In those cases with feelings of well-being and increased desire to drink this increase in blood pressure was maintained during the whole reaction. In the other cases the initial rise was followed by a fall in the diastolic pressure of 20–30 mm. Hg. Very severe reactions were marked by falls in the diastolic pressure of 40–50 mm. Hg. In cases treated with 100 mg. Temposil who at first expressed feelings of well-being and increased desire to drink and then later lost these symptoms the change in attitude was closely related to fall in blood pressure.

A state of shock was seen in 7 cases occurring approximately one hour after taking alcohol. These patients had earlier complained of shiverings and feelings of cold. On examination they were pale and worried looking with clammy sweating, rapid pulse of poor volume and falls of 40–50 mm. Hg in diastolic pressure. Five cases also showed transient irregularity of cardiac rhythm. It seems probable that the state of shock was due not only to the sudden fall in blood pressure caused by widespread vasodilation, but perhaps also to a direct toxic effect of acetaldehyde on the myocardium.

In Table III the severity of the reactions is assessed.

TABLE III

Degree of Reaction	After 50 mg. "Temposil"	After 100 mg. "Temposil"
Severe	1	14
Moderate	3	16
Slight	8	6

In the reactions graded severe, palpitation, pain and tightness in the chest, bronchospasm and shock were prominent.

In 15 cases so graded, attempts were made to assess the value of antihistamine therapy in modifying the reaction. The substance used was mepyzamine maleate (Anthisan) (N-dimethylaminoethyl-N-p-methoxy-benzyl-a-aminopyridine maleate) given intravenously in a dose of 0·05 g. In all cases there was a substantial reduction in the severity of the symptoms and signs causing distress within two to four minutes of giving the injection. Such

symptoms as palpitation, tightness and pain in the chest were rapidly eased with return of pulse rate and blood pressure to normal values. Patients who were apprehensive and worried about the outcome of the reaction became less anxious. Use of Anthisan did not appear to shorten the duration of flushing, urticaria or conjunctival injection and did little to modify headache. The efficacy of Anthisan in arresting symptoms confirms the view that part at least of the alcohol-Temposil reaction is an allergic phenomenon

Acetaldehyde reactions not interrupted lasted from 1½ to 3 hours with an average duration of two hours. Apart from continued headache the other observed symptoms and signs had settled in this period.

One case, a man aged 49, treated with 100 mg. of Temposil and the equivalent of 30 c.c. of absolute alcohol merits a short comment.

This patient had had a partial gastrectomy four years previously; following ingestion of alcohol he developed a moderate reaction after ten to fifteen minutes. Two hours later he suddenly showed a sharp drop in pulse rate from 120 to 40 per minute with a coincident fall in blood pressure from 140/90 to 70/50. He was profoundly shocked and began to vomit. Anthisan (4 c.c.) was given intravenously with little effect, but after intravenous injection of mephine (15 mg. mephentermine sulphate in 1 c.c.) blood pressure and pulse rate returned to normal values. This very delayed reaction was presumably due to the relatively rapid passage of the alcohol through the small remaining part of the stomach with subsequent slow absorption of alcohol from the small intestine and, therefore, delayed production of acetaldehyde.

In ten cases given alcohol 36 hours or more after the last dose of Temposil no acetaldehyde reaction was found. In a further 7 cases who had indulged in alcohol while on maintenance treatment it appeared from the patient's comments that they had found themselves able to drink without symptoms within 24–36 hours of the last dose of Temposil. This confirms the observation of other workers that Temposil is excreted within 24 to 36 hours (1, 5, 14).

Of the 33 patients who were given test reactions only 27 were regarded as suitable for continued treatment. Five who had shown markedly increased desire to drink after small quantities of alcohol and minimal acetaldehyde reaction were omitted. The sixth patient was an alcoholic paranoid schizophrenic who refused to take the drug.

In Table IV the results of treatment to date are briefly summarized:

TABLE IV

Time on "Temposil" in Months	No. of Patients	No. Abstinent	No. Relapsed
Less than 1 month	10	6	4
1–3 months	9	6	3
3–6 months	4	3	1
6–12 months	3	3	–
Over 12 months	1	1	–
Total	27	19	8

It would appear from the limited series we have investigated that there is a high correlation between duration of use of Temposil and abstinence from alcohol. Those patients who take the drug for periods of less than three months have considerably higher relapse rates than those who have used it for longer periods. Periods of abstinence so far range from 2 months to 15 months.

No serious side-effects of prolonged usage have been noted. Regular blood counts, urinalysis and liver function tests have been done in the majority of cases treated and no abnormalities have been detected. Two patients have complained of transient epigastric discomfort for short periods after taking the tablets. One patient had an exacerbation of longstanding acne vulgaris which settled when the dose of Temposil was reduced from 100 mg. to 50 mg. No other side-effects have been observed.

Discussion

Temposil does not produce unpleasant side-effects such as those found with disulfiram. There is, therefore, less difficulty in persuading patients to take the drug regularly.

If alcohol is taken within 24 hours of taking Temposil an acetaldehyde reaction is produced within 15 minutes. All cases in this series showed some degree of acetaldehyde reaction, whereas alcohol-disulfiram reactions are much less predictable probably due to storage of disulfiram in body fat depots (3).

Alcohol-Temposil reactions are not so severe as those found with disulfiram. The severity of the reaction can rapidly be minimized by intravenous injection of an anti-histamine, whereas disulfiram reactions are not easily modified.

In six cases who took alcohol within 24 hours of taking Temposil the interesting observation was made that when reactions developed the patients were able to reduce the intensity of the symptoms by walking about briskly. One of us (A.M.) during a test reaction not included in the above results confirmed these patients' reports that symptoms appear less prominent when an effort was made to keep walking as quickly as possible.

Only one case in this series would have been unable to walk about because of the severity of the reaction. Temposil would seem, therefore, to be a safer drug in the treatment of alcoholism than disulfiram.

The main disadvantage would appear to derive from the occurrence of increased desire to drink in the early stages of alcohol-Temposil reactions, but this difficulty can be overcome by conducting individual test reactions under close observation before beginning long-term use. It is essential to carry out these test reactions, as otherwise the alcoholic may have additional problems arising from treatment ostensibly aimed at helping him.

The above findings suggest that 100 mg. Temposil provide a more suitable dose than 50 mg. suggested by other workers.

Summary

1. The composition and mode of action of Temposil are described.

2. An analysis of 48 alcohol-Temposil reactions is made.

3. A method of modifying alcohol-Temposil reaction using anti-histaminic drugs is described.

4. Results of prolonged use in 27 patients are described.

5. Some comments are made regarding the value of Temposil in comparison with disulfiram.

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